REMARKS

Claims 1-12 are pending in the application. Claims 1-12 are rejected under USC § 112, 102(b), and/or 103(a)

The specifcation is amended on pages 6 and 24 to correct typographical errors, namely the deletion of an extra "(" on page 6 line 25 and the correction of the total number of AGUS-NOS from "N=57" to –N=157--.

Claims 1-8 and 11 are amended to clarify the relationship between a diagnosis and the distribution of MN/CA9 antigen observed on AGUS diagnosed pap smear cells. The phrase "when said MN/CA9 antigen is observed" is generally replaced by "based on the observation of said MN/CA9 antigen" to clarify that the diagnosis is not merely coincidental with the observed distribution of MN/CA9 antigen on pap smear cells. Claim 8 is amended to clarify that a characterizing fraction of an MN/CA9 protein comprises "at least one antigenic determinant or immunoreactive epitope of the MN/CA9 protein, which binds detectably to an anti-MN/CA9 antibody." Support for the amendment to claim 8 can be found in cancelled claim 10 and on page 14 lines 11-13 of the specification. Accordingly, no new matter is introduced.

Applicants hereby request further examination and reconsideration of the application, in view of the foregoing amendments and the arguments presented below.

Claim Rejections - 35 U.S.C. §112

1. Second Paragraph

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

To obtain patent protection, an inventor must set forth a claim that reasonably apprises those of skill in the art of its scope. Whether a claim is invalid as indefinite depends upon whether those skilled in the art would understand what is claimed when the claim is read in light of the specification. Orthokinetics Inc. v. Safety Travel Chairs

Inc., 806 F.2d 1565, 1576 (Fed. Cir. 1986). See also North American Vaccine v. American Cyanamid Co. 7 F.3d 1579-80 , 1365 (Fed. Cir. 1997) (The law is clear that "'[i]f the claims, read in light of the specification[s], reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more.")

The Examiner finds the recitation of "significant lesions" to be unclear. However, those of skill in the art would understand what is meant by "signficant lesions" when claims 1-12 are read in light of the specification. Applicants have explicitly described qualities or properties that allow determination of a significant lesion. See, e.g. page 8 lines 2-3 – "a significant lesion is diagnosed whenever MN/CA9 antigen is observed on atypical cells." Moreover, the metes and bounds of a significant lesion are clearly described in the specification, which explicitly distinguishes "significant lesions" from low grade lesions and a benign condition. See, e.g., page 7 lines 22-30 – "It is the distribution of MN/CA9 antigen observed on atypical or normal cells that is used to diagnose the presence of significant or low grade lesions. More specifically, significant lesions, including adenocarcinoma, invasive carcinoma (CA), or high grade squamous intraepithelial lesions (HSIL) are diagnosed when MN/CA9 antigen is observed on atypical cells. Low grade lesions, including low grade squamous intraepithelial lesions (LSIL) or atypia, are diagnosed when MN/CA9 antigen is absent from atypical cells but is present on normal endocervical cells."

Moreover, throughout the specification, the category of "significant lesions" is consistently associated with cancerous or serious pre-cancerous conditions, namely adenocarcinoma (AIS), invasive carcinoma (CA), and high grade squamous intraepitelial lesions (HSIL). See, e.g.:

> page 4 line 10 - a small fraction of the significant lesions were glandular neoplasms (AIS/CA)
>
> page 17 line 39-40 - The significant lesions can include adenocarcinoma, invasive carcinoma (CA), and high grade SIL (HSIL).
>
> page 20 line 25 - Significant Lesions = HSIL and AIS/CA

page 25 line 12 - significant lesions (HSIL and AIS/CA)

page 27 line 5 - significant lesion (HSIL and AIS/CA)

page 29 line 3 - significant lesions (HSIL and AIS)

page 29 line 15 - significant lesions (HSIL, AIS/CA)

The Examiner also found that claims 8-12 are unclear in the recitation of "a characterizing fraction." Claim 8 has been amended to clarify the meaning of "a characterizing fraction" as being "at least one antigenic determinant or immunoreactive epitope of the MN/CA9 protein, which binds detectably to an anti-MN/CA9 antibody."

In view of the foregoing amendments and arguments, Applicants respectfully traverse the rejection of claims 1-12 under 35 U.S.C. 112, second paragraph

2. First Paragraph

Claims 1-10 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the Examiner contends the specification does not enable any person skilled in the art to which is pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. More particularly, the Examiner found these claims to be overbroad because the specification enables antibody detection of MN/CA9 antigen and immunohistochemical staining with specific examples, but provides only general guidance without specific examples of in situ amplification and hybridization of MN/CA9 mRNA transcripts (see, e.g., p.16, lines 16-27).

Applicants believe one reasonably skilled in the art could readily adapt Applicant's immunological methods for detecting the expression of MN/CA9 antigen to an in situ hybridization detection method for detecting the expression of MN/CA9 mRNA, based on the disclosures in Applicants' patent application coupled with information known in the art, without undue experimentation. Nevertheless, in the interest of expediting the issuance of allowable claims, claim 12 is cancelled and claims 1,3,5-8 and 11 are amended without prejudice so the claims are no longer directed to detecting the "expression" of MN/CA9, but rather to the detection of MN/CA9 antigen *per se*. Accordingly, the claims are now commensurate in scope with antibody

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detection methods, which the Examiner has acknowledged are enabled by the specification.

Claims 2 and 8 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner objects to these claims because the specification does not provide support for claims which recite that the absence of said antigen is indicative of a disease free state. Applicants respectfully disagree. The specification clearly discloses a definite correlation between the lack of MN/CA9 immunostaining and the absence of lesions in the cervix. See, e.g. Fig. 4; p.26 line 16-17 (all cases of benign cervices had MN/CA9 negative Pap smears); p. 27 lines 1-2 (all of the benign cases were MN/CA9 negative); p. 28 lines 10-13 (A total of 29 cases were diagnosed in the AGUS-FAVOR REACTIVE category; follow up biopsies were benign in 45% (n= 13); all 13 were MN/CA9 negative); p. 28 lines 24-26 (no dysplastic tissue was identified when no immunostaining was seen); p. 29 lines 11-13 (no dysplastic lesion was observed in the 20 AGUS-NOS cases in which no MN/CA9 immunostaining was detected); p. 29 line 27 (benign histology was found for the one and only MN/CA9 negative Pap smear in the AGUS-FAVOR NEOPLASTIC category).

The Examiner cites Liao et al (1994) and Liao et al. (1996) for the proposition that not all MN/CA9 negative cases correlate with a benign condition. Few if any diagnostic methods are totally free of such "false negative" results. However, unlike the present invention, the "false negative" cases of Liao et al. (1994) were tissue specimens, not pap smear cells; and the "false negative" case of Liao et al. (1996) was an ASCUS, not an AGUS diagnosed pap smear sample. Moreover, not a single case is reported in the present application where the absence of immunostaining correlates with low grade (atypia or LSIL) or significant (HSIL or AIS/CA) lesions of the cervix. Thus, despite the Examiner's reservations about the prior art, the present application provides ample guidance, support and examples showing that Applicants' method is an improved method for distinguishing among AGUS-diagnosed pap smear samples which correlate with significant lesions, low grade lesions, and even a benign condition of the cervix.

Claim Rejections - 35 U.S.C. §102

Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Liao et al. (1996).

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

According to the Examiner, Liao et al. (1996) teach a method for determining the presence of cancerous or pre-cancerous cervical lesions from histological tissue sections comprising cells that have been cytologically diagnosed as atypical glandular cells of undetermined significance (AGUS) under the Bethesda System of terminology.

As a preliminary matter, the Bethesda System applies to pap smears, not histological tissue sections. Accordingly, the histological tissue sections of Liao et al. (1996) cannot comprise cells that have been cytologically diagnosed as AGUS. Moreover, the method of claims 1-11 determines the presence of cancerous or pre-cancerous lesions from AGUS-diagnosed pap smear cells, not tissue sections. Accordingly, Liao et al (1996) do not anticipate Claims 1-11 of the present invention.

The Liao et al. (1996) reference also reports results for 22 specimens of pap smears with cytological diagnoses of AGUS, see, e.g., Tables 4 and 5. While the Liao et al. (1996) does disclose MN antigen expression for AGUS cells, later diagnosed from histological tissue sections to be LSIL, HSIL, AIS and CA, it does not teach or suggest a method for discriminating between low grade (LSIL and atypia) and significant lesions (HSIL, AIS, and CA) by observing the distribution of MN9 antigen on AGUS-diagnosed pap smear cells as in Claim 1. Moreover, none of the pap smear cells shown in Liao et al. exhibit the honeycomb configuration, which is diagnostic of adenocarcinoma, as set forth in claims 3 and 8. In addition, Liao et al. do not teach or suggest the correlation of HSIL with MN/CA9 antigen detection on tight clusters of atypical pap smear cells (as in claims 5 and 8). Nor do they distinguish the honeycomb pattern observed for AIS from

the tight clusters observed for HSIL (as in claims 6 and 8). Finally, nowhere does Liao et al. diagnose LSIL or atypia from MN antigen detection on normal cells in the absence of staining on atypical cells as in claims 7 and 8. For all the foregoing reasons, the Liao et al reference does not anticipate the claimed invention.

Claims 1-11 are also rejected under 35 U.S.C. 102(b) as being anticipated by Liao et al. (1994). According to the Examiner, Liao et al. (1994) teach a method for determining the presence of cancerous or pre-cancerous lesions including atypical and normal endocervical cells by subjecting said cells to a procedure whereby expression of MN/CA9 antigen is detected, observing the distribution of MN/CA9 antigen expressed on the atypical or normal cells of said cytologically diagnosed cells.

Once again, as a preliminary matter, the Liao et al. (1994) reference is directed to immunohistological studies of tissue specimens and does teach subjecting AGUS-diagnosed Pap smear cells to a procedure whereby MN/CA9 antigen is detected. Moreover, the histological diagnoses of CIN I, CIN II, CIN III, AIS, and CA in Liao et al. (1994) were based on microscopic examination of samples from biopsy, conization, and hysterectomy specimens well before the tissue sections were subjected to a procedure for detecting MN/CA9 antigen.

While the Liao et al. (1994) reference does disclose detecting MN antigen in histological tissue sections from normal, low grade CIN (CIN), high grade CIN (CIN II & III), AIS, and cervical carcinomas, it does not teach or suggest a method for discriminating between low grade (LSIL and atypia) and significant lesions (HSIL, AIS, and CA) by observing the distribution of MN9 antigen on atypical or normal pap smear cells cytologically diagnosed as AGUS as in Claim 1. Moreover, Liao et al. (1994) do not teach that MN/CA9 antigen detection on pap smear cells exhibiting a honeycomb configuration is diagnostic for adenocarcinoma, as set forth in claims 3 and 8. In addition, Liao et al. do not teach or suggest the correlation of HSIL with MN9 antigen detection on tight clusters of atypical cells (as in claims 5 and 8). Nor do they distinguish the honeycomb pattern observed for AIS from the tight clusters observed for HSIL (as in claims 6 and 8). Finally, nowhere does Liao et al. diagnose LSIL or atypia

from MN antigen detection on normal cells in the absence of staining on atypical cells as in claims 7 and 8. For all the foregoing reasons, the Liao et al reference does not anticipate the claimed invention.

Claim Rejections - 35 U.S.C. §103

Claims 1-11 are rejected under 35 U.S.C.103(a) as being obvious over Liao et al. (1994). According to the Examiner, it would have been prima facie obvious to use the method of Liao et al. (1994) on pap smears because pap smears are the art standard method of diagnosis and monitoring for cervical dysplasia and cancer. However, to establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Here, there is no suggestion to modify the method of Liao et al. by selecting pap smear cells that have been cytologically diagnosed as AGUS. Pap smear cells are diagnosed as AGUS when atypical cells are observed, putatively of glandular origin, which the cytologist does not consider to be dysplasia. Accordingly, there is no expectation of success based on the art standard method of monitoring dysplastic pap smear cells. Indeed, as shown in the Tables 1 and 2 of the present application, the cytological diagnosis of AGUS correlates with significant lesions (HSIL, AIS/CA) anywhere from 15% to 58% of the time.

Unlike the Liao et al. (1994) reference, Applicants' invention recognizes and overcomes the problem of pap smears misdiagnosed as AGUS instead of LSIL, HSIL, or adenocarcinoma. Moreover, Liao et al. (1994) provides no guidance whatsoever regarding the appearance of such "atypical" cells in pap smears. Instead, Liao et al. (1994) generally detects MN/CA9 antigen in the vicinity of dysplastic or malignant tissues. Accordingly, Liao et al. do not teach or suggest detecting the presence or absence of MN9 antigen on the atypical cells of AGUS-diagnosed Pap smear cells, i.e.,

where the dysplastic nature of the cell is uncertain. Accordingly, the claimed invention would not have been obvious to one of skill in the art in view of Liao et al. (1994).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

Margaret Churchill

Date: February 28, 2001

Margaret Churchill, Ph.D.
Registration No. 39,944

Docket No. 1279-293/09905416
(213) 892-9200

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

On page 6, lines 10-27, please substitute the following paragraph:

A study of several hundred benign and neoplastic cervical specimens has shown that MN/CA9 is expressed in all cases of AIS and in more than 90% of cervical squamous neoplasms. High levels of MN/CA9 protein expression were frequently observed in the normal-looking endocervical cells in regions adjacent to dysplastic tissues but the normal cervix does not express MN/CA9 protein. In addition, a study of 305 Pap smears has also indicated that the MN/CA9 expression seen in exfoliative cells in Pap smears recapitulates MN/CA9 expression in the corresponding tissue sections of the cervix. Virtually all atypical glandular cells derived from AIS and adenocarcinoma expressed high levels of MN antigen, whereas endocervical cells obtained from benign cervices were negative (Liao SY, Brewer C, Zavada J, Pastorek J, Pastorekova S, Marietta A, Berman ML, DiSaia PJ, Stanbridge EJ. Identification of the MN antigen as a diagnostic biomarker of cervical intraepithelial squamous and glandular neoplasia and cervical carcinomas. Am. J. Pathol., 1994. 145: 598-609; [(]Liao SY, Stanbridge EJ. Expression of the MN antigen in cervical Papanicolaou smears is an early diagnostic biomarker of cervical dysplasia. Canc. Epid. Biom. Prev., 1996. 5:549-557).

On page 24 please substitute the following for Table 2.

Table 2. Biopsy Follow-Up of Patients with Cytologic Diagnosis of AGUS

Cytologic Diagnosis

	AGUS-ALL CATEGORIES N=245		AGUS-FAVOR REACTIVE N-29		AGUS-NOS N=157		AGUS-FAVOR NEOPLASTIC N=59	
Histologic Diagnosis	No.	(%)	Without SIL n=28	With SIL n=1	Without SIL n=137	With SIL n=20	Without SIL N=51	With SIL n=8
Benign	34	(14)	13	0	20	0	1	0
Atypia*	12	(5)	3	0	8	0	1	0
LSIL	76	(31)	9	1	55	2	7	2
HSIL	95	(39)	1	0	49	18	22	5
Endometrial Adenoca.	3	(1)	0	0	0	0	3	0
AIS**	25	(10)	2	0	5	0	17	1

*Atypical squamous metaplasia, atypical reserve cell proliferation, or glandular atypia.

**Coexisting early stromal invasion was seen in 3 cases.

In the claims:

Please cancel claims 10 and 12

Please amend claims 1-9 and 11 as follows:

1. (Amended) A method for determining the presence of cancerous or pre-cancerous cervical lesions from Pap smear cells that have been cytologically diagnosed

as atypical glandular cells of undetermined significance (AGUS) under the Bethesda System of terminology, said Pap smear including atypical and normal endocervical cells, said method comprising:

(A) subjecting said AGUS-diagnosed Pap smear cells to a procedure whereby [expression of] MN/CA9 antigen is detected ;

(B) observing the distribution of MN/CA9 antigen [expressed] on atypical or normal cells of said AGUS cytologically diagnosed Pap smear cells; [and]

(C) diagnosing the presence of significant lesions[, when] <u>based on the observation of</u> said MN/CA9 antigen [is observed] on said atypical cells, wherein the significant lesions include adenocarcinoma, invasive carcinoma (CA), or high grade squamous intraepithelial lesions (HSIL); <u>and</u>

(D) diagnosing the presence of low grade lesions [when] <u>based on the observation that</u> said MN/CA9 antigen is absent from said atypical cells but is present on said normal endocervical cells, wherein the low grade lesions include low grade squamous intraepithelial lesions (LSIL) or atypia.

2. (Amended) The method of claim 1, further comprising:

(E) diagnosing a benign condition [when] <u>based on the observation that</u> said MN/CA9 antigen is absent from said atypical cells and normal endocervical cells.

3. (Amended) A method for determining the presence of adenocarcinoma from Pap smear cells that have been cytologically diagnosed as atypical glandular cells of undetermined significance (AGUS) under the Bethesda System of terminology, said Pap smear including atypical and normal endocervical cells, said method comprising:

(A) subjecting said AGUS-diagnosed Pap smear cells to a procedure whereby [expression of] MN/CA9 antigen is detected;

(B) observing the distribution of MN/CA9 antigen [expressed] on atypical or normal cells of said AGUS cytologically diagnosed Pap smear cells; and

(C) diagnosing the presence of adenocarcinoma[, when] based on the observation of said MN/CA9 antigen [is observed] on said atypical cells in a honeycomb configuration.

4. (Amended) The method of claim [2] 3, wherein said adenocarcinoma is adenocarcinoma in situ (AIS) or invasive adenocarcinoma.

5. (Amended) A method for determining the presence of high grade squamous intraepithelial lesions from Pap smear cells that have been cytologically diagnosed as atypical glandular cells of undetermined significance (AGUS) under the Bethesda System of terminology, said Pap smear including atypical and normal endocervical cells, said method comprising:

(A) subjecting said AGUS-diagnosed Pap smear cells to a procedure whereby [expression of] MN/CA9 antigen is detected;

(B) observing the distribution of MN/CA9 antigen [expressed] on atypical or normal cells of said AGUS cytologically diagnosed Pap smear cells; and:

(C) diagnosing the presence of high grade squamous intraepithelial lesions (HSIL) [when] based on the observation of said MN/CA9 antigen [is observed] on said atypical cells in a tight cluster.

6. (Amended) A method for determining the presence of significant cancerous or pre-cancerous cervical lesions from Pap smear cells that have been cytologically diagnosed as atypical glandular cells of undetermined significance (AGUS) under the Bethesda System of terminology, said Pap smear including atypical and normal endocervical cells, said method comprising:

(A) subjecting said AGUS-diagnosed Pap smear cells to a procedure whereby [expression of] MN/CA9 antigen is detected;

(B) observing the distribution of MN/CA9 antigen [expressed] on atypical or normal cells of said AGUS cytologically diagnosed Pap smear cells;

(C) diagnosing the presence of significant lesions[, when] based on the observation of said MN/CA9 antigen [is observed] on said atypical cells, wherein the significant lesions include adenocarcinoma, invasive carcinoma, or high grade intraepithelial lesions;

(D) diagnosing the presence of adenocarcinoma[, when] based on the observation of said MN/CA9 antigen [is observed] on said atypical cells in a honeycomb configuration; and

(E) diagnosing the presence of high grade squamous intraepithelial lesions (HSIL) [when] based on the observation of said MN/CA9 antigen [is observed] on said atypical cells in a tight cluster.

7. (Amended) A method for determining the presence of low grade cervical lesions from Pap smear cells that have been cytologically diagnosed as atypical glandular cells of undetermined significance (AGUS) under the Bethesda System of terminology, said Pap smear including atypical and normal endocervical cells, said method comprising:

(A) subjecting said AGUS-diagnosed Pap smear cells to a procedure whereby [expression of] MN/CA9 antigen is detected;

(B) observing the distribution of MN/CA9 antigen [expressed] on atypical and normal cells of said AGUS cytologically diagnosed Pap smear cells; and

(C) diagnosing the presence of low grade squamous intraepithelial lesions (LSIL) or atypia [when] based on the observation that said MN/CA9 antigen is absent from said atypical cells but is present on said normal endocervical cells.

8. (Amended) A method for determining the presence or absence of cancerous or pre-cancerous cervical lesions from Pap smear cells that have been cytologically diagnosed as atypical glandular cells of undetermined significance (AGUS) under the Bethesda System of terminology, said Pap smear including atypical and normal endocervical cells, said method comprising:

(A) subjecting said AGUS-diagnosed Pap smear cells to a procedure whereby [an MN/CA9 protein or] a characterizing fraction [thereof,] of an MN/CA9 protein is detected, said characterizing fraction comprising at least one antigenic determinant or immunoreactive epitope of the MN/CA9 protein, which binds detectably to an anti-MN/CA9 antibody; and

(B) observing the distribution of MN/CA9 antigen [expressed] on atypical or normal cells of said AGUS cytologically diagnosed Pap smear;

(C) diagnosing the presence of adenocarcinoma, [when] based on the observation of said MN/CA9 antigen [is observed] on said atypical cells in a honeycomb configuration;

(D) diagnosing the presence of high grade squamous intraepithelial lesions (HSIL) [when] based on the observation of said MN/CA9 antigen [is observed] on said atypical cells in a tight cluster;

(E) diagnosing the presence of low grade squamous intraepithelial lesions (LSIL) and/or atypia [when] based on the observation that said MN/CA9 antigen is absent from said atypical cells but is present on said normal endocervical cells; and

(F) diagnosing a benign condition [when] based on the observation that said MN/CA9 antigen is absent from said atypical cells and normal endocervical cells.

9. (Cancel) The method of claim 8, wherein said MN/CA9 antigen comprises a characterizing fraction of an MN/CA9 protein.

10. (Cancel) The method of claim 9, wherein said characterizing fraction of said MN/CA9 protein comprises at least one immunoreactive epitope of said MN/CA9 protein.

11. (Amended) The method of claim 8, wherein said [expression] MN/CA9 antigen is detected by immunohistochemistry.

12. (Cancel) The method of claim 8 wherein said expression is detected by amplification and/or hybridization of mRNA transcripts encoding MN/CA9 protein.